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# UNIVERSITÀ DEGLI STUDI DI TORINO

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## **SURGICAL REMISSION OF CUSHING'S SYNDROME REDUCES CARDIOVASCULAR RISK.**

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## **ABSTRACT**

**Objective:** Recent studies questioned the reversibility of complications of Cushing's syndrome (CS) after successful surgical treatment. Aim of the study was to assess the outcome of patients with CS who achieved disease remission compared to those patients with persistent hypercortisolism and matched controls.

**Design:** Retrospective study of 75 patients with CS followed at an academic center.

**Methods:** Cardiovascular risk profile was evaluated in 51 patients with CS in remission (group 1) and 24 patients with persistent disease (group 2) and compared with 60 controls. Mortality of patients with CS was compared to background population.

**Results:** In group 1, the frequency of cardiovascular risk factors dropped after disease remission even if remained higher at the last follow up than in control group. In group 2, the frequency of cardiovascular risk factors remained unchanged during follow up. Cardiovascular and thromboembolic events rate was higher in group 2 than in group 1, as was mortality rate (2 deaths in group 1 and 9 in group 2; ratio of SMR, 0.11; 95% C.I., 0.011- 0.512). Survival was significantly longer in group 1 than group 2 (87 months, 80-98 vs. 48 months, 38-62;  $p < 0.0001$ ).

Conclusions: Successful surgical treatment of hypercortisolism improves significantly cardiovascular risk and may reduce mortality rate. Patients with persistent disease have increased morbidity and mortality than patients in remission.

## INTRODUCTION

Endogenous hypercortisolism may have severe consequences and cause a number of complications, including obesity, hypertension, hyperglycemia, dyslipidemia and thrombophilia (1-4). Cushing's syndrome is indeed considered as an archetype of the metabolic syndrome (5) since insulin resistance and the accompanying spectrum of clinical features may occur in about two thirds of patients (1,2,6). Thus, it is not surprising that chronic glucocorticoid excess does significantly affect quality and duration of life (7), primarily for cardiovascular disease causing a two to four-fold increase in mortality compared to the general population (8-13). The evidence that Cushing's syndrome is associated with an increased mortality calls for an early diagnosis and prompt cure of hypercortisolism (14). However, diagnosis is often delayed because the clinical phenotype of hypercortisolism overlaps that of the metabolic syndrome (1,3,4,15) since the so-called specific Cushingoid features are slight or lacking in many patients, particularly when the entity of cortisol excess is mild (16,17). This is an issue of particular relevance, since mild Cushing's syndrome may be more common than previously thought, especially among patients with type 2 diabetes and metabolic syndrome (18,19,20). In addition, recent studies questioned the reversibility of complications due to hypercortisolism after its surgical treatment (2,21,22,23,24). These findings suggest that an increased cardiovascular risk may persist despite successful treatment of cortisol excess influencing negatively health outcomes in patients who have suffered from Cushing's syndrome.

The aim of this study was to investigate the outcome of patients with Cushing's syndrome of benign etiology after attainment of disease remission compared to patients with persistent hypercortisolism and background population.

## SUBJECTS and METHODS

### *Patients*

This retrospective study includes and analyses data of patients suffering from endogenous Cushing's syndrome (CS) who have been followed by our institution, a university referral centre for endocrine diseases. All these data were retrieved by medical records from January 1991 through December 2010. Follow up for this report ended in December 2011. A total of 92 patients with CS of benign etiology were identified. Among these, 1 patient with pituitary-dependent CS died within few months from the diagnosis and was excluded, 1 was on dialysis and was also excluded, while 15 patients were lost to follow-up (Figure 1). The excluded ones were 4 men and 13 women, with a median age of 68 years (range, 58-75 years). Etiology of CS was pituitary-dependent in 13 cases, adrenal-dependent in 4 cases. The study cohort included 75 patients, of whom 50 (67%) with pituitary-dependent CS (CD), 19 (25%) with adrenal-dependent CS (ACS), and 6 (8%) with ectopic ACTH syndrome (EAS) caused by a benign neuroendocrine tumour (3 differentiated neuroendocrine tumors, 3 occult ectopic). CD was due to a pituitary microadenoma in all but one case. Among the study patients, 51 (68%) achieved remission of hypercortisolism while 24 (32%) had persistent disease (Figure 1).

The diagnosis of CS was based on clinical features and endocrine workup according to a standard protocol validated at our university centre (25). Diagnosis of CS was made in presence of at least 2 of the following findings: 1) increased daily urinary free cortisol (UFC) excretion, 2) failure to suppress cortisol after 1 mg overnight dexamethasone suppression test (**1 mg-DST**), 3) elevated midnight serum or salivary cortisol (MSC). Cut off values of these tests have been previously reported (26). The differential diagnosis of CS among CD, EAS and ACS was made on the basis of ACTH levels, overnight 8-mg dexamethasone suppression test (HDDST), corticotrophin-releasing hormone (CRH) stimulation test, and appropriate imaging studies depending on the results of hormonal workup, according to a standard protocol validated at our center (27). Bilateral inferior petrosal sinus sampling for ACTH measurement was performed in patients with

ACTH-dependent CS in whom clinical, biochemical and radiological studies were discordant or equivocal. Published criteria for central to peripheral ACTH gradients were used to diagnose a non-pituitary source of ACTH (28). None of the patients had been given any drug known to affect the hypothalamic-pituitary-adrenal axis, neither reporting a current or previous history of either alcohol abuse or major mood disorders requiring psychiatric assistance. Diagnosis of CD has been confirmed by pathological findings and/or post-operative biochemical evidence of hypoadrenalism, or longstanding normalization of UFC, MSC and **1 mg-DST** in all but 6 patients who did not undergo surgery and in whom diagnosis was based on results of dynamic tests, imaging and IPSS. Diagnosis of ACS was histologically confirmed in all but 3 patients who refused surgery, in whom it was based on hormonal and imaging data. Diagnosis of EAS was histologically confirmed in 3 patients (bronchial neuroendocrine tumor), while the ACTH-secreting tumor remained occult in 3 patients, in whom the diagnosis was based on results of dynamic tests and IPSS.

Patients were studied at diagnosis and then entered a program of proactive follow-up for at least 12 months. Duration of hypercortisolism was considered in the period of time between the date of diagnosis and that of surgery, when remission of hypercortisolism was attained, or date of the last follow-up for patients who did not attain remission. This definition underestimates the actual duration of hypercortisolism, since it does not take into account a variable delay in diagnosis which is difficult to assess precisely in a retrospective analysis. Remission of CS was defined by resolution of cushingoid signs along with post-operative adrenal insufficiency or normalization of all hormonal tests including suppression of cortisol <50 nmol/l after a **1 mg-DST**. Based on the above mentioned criteria, 51 patients were considered to be in remission at the last follow-up (group 1), while 24 patients had persistent hypercortisolism (group 2). Sixty patients with pituitary incidentaloma were also included in the study as controls. Patients in disease remission (group 1) were younger than either patients with persistent disease (group 2) ( $39.6 \pm 15.6$  yrs vs  $54.2 \pm 16.3$  yrs,  $p=0.001$ ) or controls (group 3) ( $39.6 \pm 15.6$  yrs vs  $48.2 \pm 14.4$  yrs,  $p=0.009$ ). The institutional review board approved the study and all patients gave their informed consent in order to take part in the study.



#### *Group 1 (patients in disease remission) (Figure 1)*

This group included 51 patients in remission at the last follow-up, 10 men (20%) and 41 women (80%) aged between 14 and 72 years (median, 36). Of these, 33 patients had CD (65%), 15 had ACS (29%), of whom 11 adrenal adenoma and 4 ACTH-independent macronodular adrenal hyperplasia (AIMAH), and 3 had EAS (6%) sustained by a bronchial benign neuroendocrine tumor. Median duration of follow-up after remission was 56.5 months (range, 12-192). Median duration of hypercortisolism was 6 months (range 1-67). All patients with CD underwent transsphenoidal surgery; 9 patients required a second surgery and 8 needed also bilateral adrenalectomy. Two CD patients underwent pituitary radiotherapy and only 2 patients underwent medical treatment with ketoconazole or cabergoline for a short period before surgical treatment. Median duration of steroid replacement was 12.5 months (range, 1-192). Steroid replacement was done with cortisone acetate at the starting dose of 25 mg/m<sup>2</sup>. The dose was then down-titrated based on clinical presentation, biochemistry and serum cortisol measurement. Among the ACS patients, 11 required monolateral adrenalectomy and 4 bilateral adrenalectomy. The patients with EAS underwent resection of the ACTH-secreting tumor.

#### *Group 2 (patients with persistent disease) (Figure 1)*

This group included 24 patients with active hypercortisolism at the last follow-up, 7 men (29 %) and 17 women (71%), aged between 26 and 79 years (median, 60). Seventeen of these had CD (71%), 4 ACS (17%) due to ACTH-independent macronodular adrenal hyperplasia and 3 EAS (12 %) due to occult ACTH secreting tumor. Median duration of follow-up (and hypercortisolism) was 24 months (range 12-201). Among those patients with CD, 11 underwent transsphenoidal surgery (surgery was repeated 3 times in 1 patient and 2 times in 1), while the remainders did not consent to surgery (n=5) or were not fit to surgery (n=1). After surgical failure, 8 patients had been treated with medical therapy, 1 with gamma knife radiosurgery, while 2 of them refused further treatment. The 6 CD patients who did not undergo surgery were treated with ketoconazole that was discontinued in 5 patients for unwanted effects. The patients with ACS refused

bilateral adrenalectomy (monolateral adrenalectomy was done in 1 patient) and two of them were treated with ketoconazole. The 3 patients with occult EAS underwent medical therapy (ketoconazole plus somatostatin analog).

### *Group 3 (control subjects)*

This group included 60 patients with non-functioning pituitary microadenoma discovered serendipitously (pituitary incidentaloma) referred to the outpatient clinic of our institution during the period 2000-2010. They underwent MRI for headache or vertigo. Pituitary function was normal in these patients who served as controls to determine hypertension, diabetes and obesity frequency in a background population. They were 15 men (25%) and 45 women (75%), aged between 18 and 80 years (median, 49).

## **Study protocol**

### *Clinical evaluation*

For all subjects, weight, height, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were evaluated. A BMI of 25–30 kg/m<sup>2</sup> was considered as an index of overweight; a BMI above 30 kg/m<sup>2</sup> was considered as an index of obesity (29). The waist was measured as the minimum abdominal circumference between the xiphoid process and the umbilicus; waist above 88 cm in women and 102 cm in men defined central obesity (30,31). According to the ESH and ESC 2007 guidelines (32), blood pressure was measured in the non-dominant arm, with subjects in a relaxed sitting position, using a mercury sphygmomanometer placed at heart level; the average of three measurements was calculated. Hypertension was diagnosed when SBP values were  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg, or whether anti-hypertensive treatment was instituted, and was graded according to the ESH and ESC 2007 guidelines (32).

Cardiovascular events, defined as myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack (TIA) or other arterial thromboembolic events, were ascertained by reviewing patients' history, discharge summaries and source documents; complementary documentation was requested if necessary. Venous thromboembolic events, defined as deep vein thrombosis or pulmonary embolism were ascertained using the same method. Smoking status was defined as positive if patients were current or former smokers while only occasional consumption of alcoholic beverages was reported in some patients.

### *Biochemical evaluation*

Fasting glucose, triglycerides, total, LDL, and HDL cholesterol were measured by standard procedures. Diabetes mellitus was diagnosed when fasting blood glucose levels were 7 mmol/l or greater in two consecutive determinations or at least 11.1 mmol/l 2 h after an oral glucose load. Impaired fasting glucose (IFG) was diagnosed when fasting glucose was between 6.1 mmol/l and 7 mmol/l in at least 2 samples

collected in different days (33,34). Hypertriglyceridemia was diagnosed when triglyceride levels were above 1.69 mmol/l, whereas hypercholesterolemia was diagnosed when LDL cholesterol levels were above 4.13 mmol/l and low HDL when HDL cholesterol levels were under 1.03 mmol/l (30,31) .

Hormones were measured in-house with commercially available reagents. All samples for an individual subject were batched and run in duplicate. Serum, salivary and urinary cortisol were measured using commercially available RIAs. Plasma ACTH was measured by commercially available immunoradiometric assays. Intra- and interassay coefficients of variation for all hormone variables were less than 10% and 15%, respectively.

Clinical, biochemical and hormonal assessment was performed at diagnosis and every six months during follow-up. Death certificates and medical records verified death causes.

#### *Statistical analysis*

Descriptive analysis were performed for categorical and continuous data. When data are expressed as percent values, these refer to valid cases. Kolmogorov–Smirnov test was used to assess normal distribution of continuous variables. Parametric two-tailed Student's t-test and non parametric Mann–Whitney U test were used to analyse the differences for normally and non-normally distributed continuous variables, respectively. The Chi-square and Fisher's exact test were used to analyse the differences for categorical variables. Levels of statistical significance were set at  $P < 0.05$ .

Standardized mortality ratios (SMR) and relative 95% confidence intervals (95% CI) were calculated for group 1 and group 2 using mortality data of the general population of our region, Piedmont counting about 4.5 million inhabitants, as reference (Banca Dati Demografica Evolutiva -Regione Piemonte <http://www.regione.piemonte.it/stat/bdde/info/principi.htm>). In order to compare mortality between groups, the ratio of the two SMRs (RSMR) and relative 95% CI was computed (35).

Survival analysis was performed using Kaplan Meier curves and relative Log-Rank tests. A Cox model was carried out to adjust the results for the principal confounding factors.

All statistical analysis were operated using the Stata statistical software (StataCorp. Statistical Software: Release 7.0. College Station, TX: Stata Corporation. 2001).

## RESULTS

### *Group 1 (disease remission)*

Clinical characteristics of the patients either at diagnosis or at the time of last follow-up are given in Table 1. In this group, 1 deep vein thrombosis, and 3 cardiovascular events (1 unstable angina requiring percutaneous transluminal coronary angioplasty and 2 myocardial infarctions) occurred before diagnosis of Cushing. Furthermore, 1 patient had deep vein thrombosis while awaiting surgery, while 1 stroke and 1 pulmonary embolism were recorded in the early post-operative period. After remission, 1 patient had myocardial infarction and 1 pulmonary embolism. Two patients died of colorectal and gallbladder cancer, respectively; 10 patients (19.6%) developed hypopituitarism. Pituitary deficiencies underwent hormone replacement according to the existing protocols available at the time. All the patients had TSH deficiency and were put on 75-100 mcg/d l-thyroxine, two hypogonadal men were given 250 mg testosterone enanthate IM every two weeks and two women were on transdermal estrogen plus oral progesterone. Moreover, five patients were put on recombinant growth hormone replacement therapy at doses ranging from 0.02 to 0.05 mg/kg/week. None of the patients developed clinical or biochemical signs of under- or over-replacement.

### *Group 2 (active disease)*

Clinical characteristics of the patients either at diagnosis or at the time of last follow-up are given in Table 1 and Table 2. In this group, 1 cardiovascular event and 1 thromboembolic venous event were observed before the diagnosis. During follow-up, 4 myocardial infarctions, 1 stroke, 1 deep vein thrombosis and 1 pulmonary embolism were observed. Nine patients (37%) died, of whom 4 from cardiovascular events, 3 from sepsis, 2 from malignancies. Three patients who underwent pituitary surgery developed TSH deficiency (14%) and were put on 75-125 mcg/d l-thyroxine. Primary hypogonadism was diagnosed in 2

men who were treated with testosterone replacement therapy (250 mg testosterone enanthate IM every two weeks).

#### *Changes in cardiovascular risk factors and mortality*

In group 1, the frequency of all cardiovascular risk factors dropped significantly after disease remission and the percentage of patients achieving target levels for blood pressure and HbA1c increased remarkably (Table 1). However, the frequency of diabetes, central obesity and dyslipidemia at the last follow-up remained higher than in the control group (Table 1). In group 2, the frequency of cardiovascular risk factors did not change, or increased, from baseline to the last follow-up remaining greater than that of controls (Table 1). The percentage of patients achieving target levels for blood pressure and HbA1c did not change remarkably during follow-up (Table 1).

The rate of cardiovascular and thromboembolic events during follow-up was higher in group 2 than in group 1 (29.2% vs. 3.9%;  $p=0.006$ ), notwithstanding that duration of follow-up was longer for group 1. Death was observed in 9 patients (37%) of group 2 (SMR = 2.56; 95% C.I., 0.76 - 3.06), of whom 7 were from causes possibly related to cortisol excess, and in 2 patients (4%) of group 1 (SMR = 0.28; 95% C.I., 0.13 - 2.22) for unrelated causes. Assessment of the ratio of the 2 SMRs confirmed the reduced mortality risk in patients attaining disease remission (RSMR = 0.11; 95% C.I., 0.011- 0.512).

The survival analysis demonstrated a median survival of 87 months (95% C.I., 80-98 months) in group 1 and 48 months (95% C.I., 38-62 months) in group 2, respectively. Kaplan Meier curves showed a difference between groups for all follow-up time, with a survival probability at the end of follow-up of 75% in group 1 and 48% in group 2, respectively (Log-Rank test=17.96,  $p<0.0001$ ) (Figure 2). The results of the mortality ratio and the survival probability continue to show a statistically significant difference between the groups after adjustment for age and sex.

## DISCUSSION

Chronic hypercortisolism causes a number of associated features, such as hypertension, central obesity, hyperglycemia, dyslipidemia, thrombophilia, that determine an elevated cardiovascular risk (1). The present study confirms that central obesity and hypertension are the most frequently observed complications, being found in 82% and 63% of patients at diagnosis, respectively. In our cohort, hypertension was usually slight to moderate, but often resistant to treatment, since only 44% of patients had blood pressure at target. Dyslipidemia was also common, presenting as reduced HDL cholesterol and mixed dyslipidemia in most cases. Overt diabetes was found in 27% of patients with target HbA1c levels attained in about one third only. These observations fit completely with the clinical presentation reported by ERCUSYN (European Register on Cushing's Syndrome), a large European database including 481 patients of different etiologies (36). The clustering of multiple cardiovascular risk factors observed in the majority of our patients, as it is usual for Cushing's syndrome (2), may confer a high probability of future cardiovascular events. However, in Cushing's syndrome the risk profile is not explained completely by the conventional risk factors but also by disease-specific factors that are still inadequately defined and partly related to a hypercoagulable state (37-39).

Interestingly, these risk factors reverted following remission of hypercortisolism in a significant number of patients; thus, on average, surgical cure was able to abate significantly the cardiovascular risk of Cushing patients. Conversely, in patients with persistently active Cushing the overall cardiovascular risk remains unchanged. Furthermore, lower frequency of cardiovascular and venous thromboembolic events was recorded in patients who underwent remission compared to those patients with persistently active disease, as a clear demonstration of benefit of resolved hypercortisolism. These findings are consistent with a cortisol-induced activation of coagulation and demonstrate the beneficial effects that can be attained with elimination of hypercortisolism (2, 37-40). However, our data confirm that risk of venous thromboembolic events is not limited to the early post-operative period (3).



In our cohort, the benefits of surgery were more apparent than previously reported in two series of 25 and 29 patients, respectively, assessed 1 year following remission (22,24). We observed normalization of body weight, blood pressure and lipid levels in higher percentages of cases, whereas figures for diabetes were similar. It is possible that a progressive improvement in the metabolic profile may develop with a longer follow-up after resolution of hypercortisolism (41), although there are studies showing that cardiovascular risk remains high after many years (7, 13, 21). Improvement may require time particularly in patients given postoperative replacement. Duration of glucocorticoid replacement might be long (the median was 12.5 months in our cohort) and some patients in the previous series were still on replacement at the time of assessment (22,24). This condition may contribute to the residual cardiovascular risk since it is known that conventional glucocorticoid replacement may induce metabolic alterations in hypopituitary patients, even if it has received scarce attention (42).

Some patients refused surgical treatment although it has been strongly recommended for all of them, in particular when bilateral adrenalectomy was considered (i.e. in case of AIMAH.) An incomplete compliance with surgical recommendations has been already observed. Only 66% of CD patients studied by Yaneva et al. underwent TSS as first line treatment, and 36% of patients with AIMAH refused surgery (43).

Other factors predicting a worse outcome after surgery are the use of pituitary radiotherapy, that is a known risk factor of mortality in patients with pituitary tumors (44), and development of pituitary hormone deficiencies, that also portends increased mortality. Treatment of hypopituitarism is a major clinical problem and replacement therapies may per se worsen the cardiovascular risk profile (42). In our cohort, pituitary radiotherapy was rarely used and pituitary deficiency less frequently observed than in previous series (13, 22, 24). The incidence/frequency of hormone deficiencies was comparable between patients in remission or with disease persistence, as was the modality of replacement. The number of patients is too small to assess the contribution of replacement therapies to patient's outcome. It is pertinent to consider that studies showing persistence of metabolic and cardiovascular damage have included only patients with pituitary-dependent Cushing (13, 22,23) and, as Giordano and coworkers (24) nicely pointed out, such

patients may be characterized by a less favorable outcome than patients with cortisol secreting adrenal adenoma for the above-mentioned considerations.

After normalization of cortisol excess, all the risk factors returned to a level comparable to control subjects, apart from obesity and triglyceridemia (which may itself relate directly to central obesity), as previously observed (23, 24, 41). The comparison with a control group including patients who had to seek medical advice is a more appropriate match than normal volunteers, to avoid the healthier comparator bias, and strengthens the value of observing a residual cardiovascular risk. Although analyses have been adjusted for the age difference, we disclose as a limit group 1 patients younger age. Older age implies, obviously, a higher risk of death and may be associated with a reduced probability to get into remission (13, 43, 45). In our study, patients with persistent disease showed increased mortality than patients in remission, whose mortality rate was comparable to the reference population, despite the fact that their cardiovascular risk was not completely normalized following resolution of hypercortisolism. However, we should be cautious concluding that successful treatment of hypercortisolism restores mortality risk to the level of the reference population. In this case, a longer follow-up may be needed to unmask a slight rise in mortality rate due to residual cardiovascular risk. Usually previous studies with longer follow-up date back to the sixties or seventies, when treatment of hypercortisolism was much different, particularly for the frequent use of pituitary radiotherapy, that is an independent predictor of morbidity and mortality (44).

The issue whether cure of Cushing may reset excess mortality associated with the condition at levels observed in the background population remains controversial. A Danish survey showed that a higher mortality rate is confined to patients in whom cure was not achieved, whereas in patients free of disease it is comparable with the general population (8). In addition, a Dutch study confirmed a significant increase in standard mortality ratio only in CD patients with persistent disease (12). On the contrary, a survey in New Zealand showed that chronic cortisol excess is associated with excess mortality notwithstanding the high number of patients who achieved cure during follow-up (11). A single-center study leaded in UK confirmed that the higher death risk of CD does not completely revert to normal level after resolution of hypercortisolism. However, patients with disease remission had a far better outcome than those ones with

persistence of hypercortisolism (10). A recent contribute to this conflicting topic is a population-based study showing that successful surgery does not normalize cardiovascular and mortality risk in a cohort of operated patients only (13).

This existing discrepancy may be explained by a number of factors, such as low number of observed deaths, variable duration of follow-up, heterogeneous inclusion criteria (i.e. selection of CD patients only), different modalities of data extraction (national registries, institutional records, ect), and variable, and often unclear, definition of remission. A recent meta-analysis concluded that CD patients in remission do not appear to have an increased mortality than the reference population, although the statistical power of this analysis was limited (46).

Strengths of our study are the inclusion of all patients with Cushing's syndrome followed proactively at a single center, with a clear definition of disease remission and careful recording of cardiovascular and thromboembolic events. We think that population-based studies have the advantage of larger series but information on biochemical data and cure after surgery may not be so detailed as in reports of monocentric cohorts. However, we recognize the limits of a retrospective analysis of a small cohort size including different etiologies of Cushing. In this real life setting the two group presented different age (in favor of a possible increased cardiovascular risk in persistent Cushing patients) and follow-up, that does not influence the results since a greater number of cardiovascular events and deaths occurred in the group of patients with a shorter follow-up.

To conclude, our study shows that resolution of hypercortisolism induces a significant improvement in a number of cardiovascular risk factors, such as hypertension, diabetes, obesity and dyslipidemia. Still, these conditions remain more evident than in control subjects in agreement with the concept of a residual cardiovascular risk after disease remission. These findings do not downplay the importance of attaining cure as quickly as possible and by no means make an argument against surgery, since in our series successful surgical treatment of hypercortisolism may reduce mortality rate. However, our study cannot demonstrate that mortality after cure is comparable to that of the reference population.

Declaration of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported

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